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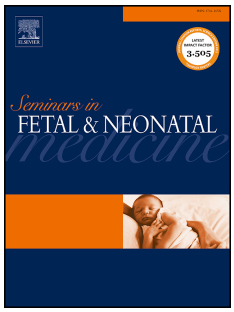

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PII: S1744-165X(18)30035-0

DOI: 10.1016/j.siny.2018.02.005

Reference: SFNM 937

To appear in: *Seminars in Fetal and Neonatal Medicine*

Please cite this article as: Stevenson NJ, Vanhatalo S, Designing a trial for neonatal seizure treatment, *Seminars in Fetal and Neonatal Medicine* (2018), doi: 10.1016/j.siny.2018.02.005.

Designing a trial for neonatal seizure treatment

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SUMMARY

Neonatal seizures are widely considered a neurological emergency with a need for prompt treatment, yet they are known to present a highly elusive target for bedside clinicians. Recent studies have suggested that the design of neonatal seizure treatment trial design will profoundly influence the sample size, which may readily increase to hundreds or even thousands, while the achieved effect size may diminish to clinical irrelevance. The self-limiting and rapidly resolving nature of neonatal seizures diminishes the achievable treatment effect every hour after seizure onset and measured effects may be confused with spontaneous resolution, precluding the value of many observational studies. The large individual variability in seizure occurrence over time and between etiologies challenges group comparisons, while the absence of clinical signs mandates quantification of seizure occurrence with continuous multi-channel EEG monitoring. A biologically sound approach that views neonatal seizures as a functional cot-side biomarker rather than an object to treat can overcome these challenges.

Keywords:

Status epilepticus

Antiepileptic drug

Randomized control trial

Episodic illness

Migraine

Infection

1. Introduction

Seizures are common in newborns treated in the neonatal intensive care unit (NICU), and are usually considered to require prompt treatment. The recent introduction of continuous video electroencephalography (EEG) monitoring of at-risk infants has made it clear that diagnosing neonatal seizures, treating them and following up treatment effects present highly elusive targets for bedside clinicians [1–5]. It is now known that clinical recognition of neonatal seizures is challenging, or even ambiguous at times, and neonatal seizures vary widely with respect to underlying etiology, clinical presentation, and natural time-course, and have implications for neurocognitive prognosis [6–10].

Developing evidence-based guidelines for drug treatments calls for studies that measure drug effects quantitatively and against an alternative treatment or placebo. In general, the ability of a trial to demonstrate treatment success will be highly dependent on design. When designing a trial on neonatal seizure treatment, the most important choices include (i) the clinically relevant outcome measure(s), (ii) the control group, and (iii) the level of desired efficacy. Trial design must also strike a compromise between clinical traditions and practical considerations regarding logistical constraints [11]. To the best of our knowledge, there are no trials on neonatal seizure treatment that provide an evidence-based sample size calculation based on the characteristics of neonatal seizure occurrence. This is entirely understandable as detailed knowledge of the time-course of neonatal seizures has only recently become available [8].

In this review, we will first briefly describe the challenge associated with neonatal seizure studies, followed by a brief introduction as to how these challenges could be addressed in future trials. Finally, we suggest different approaches, including alternative attitudes towards clinical perception and handling of neonatal seizures, in order to replace ambiguous treatment traditions with evidence-based, individualized medicine.

2. Trials of neonatal seizure treatment

A review by Booth and Evans found that only two randomized controlled trials (RCTs) for the treatment of neonatal seizures met their selection criteria [12]. Painter et al. compared the effectiveness of phenobarbital and phenytoin for the reduction of neonatal seizures in a cohort of 59 neonate. The primary outcome measure was complete ‘seizure control’ (no seizure burden) observed in the EEG after the target plasma level of free drug had been achieved [13]. They found that both phenobarbital and phenytoin controlled seizures in approximately 60% of subjects and that there was no difference in effect between these drugs. Boylan et al. compared the effectiveness of lidocaine and midazolam/clonazepam as a second-

line neonatal seizure treatment in a cohort of 11 neonates (with phenobarbitone as a first line) [14]. The primary outcome measure was again 'seizure control', which was defined as the reduction of seizure burden in the EEG of more than 80% compared to a pre-treatment baseline. They found seizure control in 60% of neonates treated with lidocaine and no neonates treated with benzodiazepines; however, they did not analyse group differences due to the small sample size. These trials show that whereas it may be possible to measure the short-term efficacy of a drug treatment for neonatal seizures in a relatively small cohort of neonates achievable in real-life trial scenarios, it is much more difficult, although necessary, to determine whether one drug is more effective than another (RCTs with a positive control) – a proposition that more closely achieves clinical equipoise [15].

Attempts to reinvigorate the pursuit of viable neonatal seizure treatments inspired several observational studies of neonatal seizure treatment [16–19]. A large multi-center RCT of bumetanide was stopped early due to suspicion of adverse effects [11]; a thorough post-hoc reassessment of its findings, together with other recent literature, led to the ideas presented in this review paper. Nevertheless, in the 14 years since the review of Booth and Evans, the studies of Painter et al. and Boylan et al. remain the only completed RCTs of neonatal seizure treatment nearly two decades after their completion [13,14].

3. EEG monitoring is obligatory, not optional

Visual interpretation of the multi-channel EEG is the reference standard for the detection of neonatal seizures. The clinical manifestation of seizures is highly variable, ranging from no overt clinical signs (also known as subclinical or electrographic) to a myriad of behaviours that may readily be confused with non-epileptic movement [6,7]. Electroclinical dissociation is also common whereby seizures that initially have clinical correlates become electrographic only after neonatal seizure treatment [20,21]. It has been well known for decades from older patient groups that the clinical manifestation only reflects the functional cortical anatomy of ictal discharge. There is, hence, no biological rationale in making therapeutic distinction between seizures with or without clinical signs.

Outcome measures for neonatal seizure treatment must, therefore, be based on the visual interpretation of the multi-channel EEG. The least-biased objective measure of seizures for trial outcome is seizure burden, i.e. the accumulated duration of seizure during a period of interest [5,13,14,22].

It is important to note that seizure detection via visual interpretation of the multi-channel EEG is not perfect. There are inter- and intra-rater differences in EEG interpretations and the EEG only records the activity at the cortical surface, not the deeper structures of the brain [5,22,23]. There are several steps investigators can take to ensure homogeneity of EEG

monitoring and quality of seizure detection throughout a trial. The first is the use of a common electrode placement, as assessment of seizure burden can vary with respect to electrode position and the number of electrodes used [23–25]. The annotation of the EEG should also be undertaken by several reviewers (ideally the same set of reviewers for each subject) who are fully blinded to the trial groups and the timing of clinical events to ensure that the variability of EEG interpretation (subjectivity) can be incorporated into the statistical analysis of drug efficacy. Subsequent statistical analysis would then be performed either by using the resulting consensus annotations or with multivariate hypothesis test for correlated variables such as Hotelling's T-square test [11,26].

The necessity for obtaining EEG recording from as early, and as long, as possible, sets significant challenges to trial logistics. Setting up and maintaining a good quality recording is easier with a reduced number of EEG electrodes, whereas seizure analysis is more comprehensive with more complex recordings [23–25]. Direct comparison of visual seizure detection from different numbers of recording electrodes suggests that the often-used four-channel EEG recording may be an appropriate solution for striking a compromise between these interests [23].

Automated seizure detection algorithms could offer an alternative to EEG interpretation [27,28]. Their cot-side implementation could accelerate patient recruitment, which is crucial for reducing the delay between seizure onset and treatment (see Fig. 1). In addition, automated detection would offer an objective alternative to the requirement of labor-intensive, EEG interpretation by multiple human raters.

4. Seizures are self-limiting, and not all seizures are created equal

It is now well accepted that most seizures in a neonate occur as transient reactions to an acute cerebral compromise (asphyxic, ischemic, acute metabolic, infectious). Their onset is typically within first days of life, their intensity reflects the underlying cerebral damage, and they tend to resolve within tens of hours after onset irrespective of treatment efficacy (see Fig. 2) [8,29,30]. In contrast, neonatal seizures due to metabolic and/or genetic origin (e.g. the neonatal-onset epilepsies) may manifest at more variable times after birth with a time-course that no longer spontaneously resolves, and their responses to treatment as well as long-term prognosis are determined by the specific underlying molecular pathologies [31–33].

These considerations together mean that electroclinical signatures and characteristic time-courses of neonatal seizures are too variable between etiologies to allow for a trial design that combines them, irrespective of the selected outcome measures. Effective, tailored treatments for acute symptomatic neonatal seizures will be distinct from strategies to treat neonatal epilepsies. Stratification according to the multiple acute symptomatic etiologies

would require scaled-up recruitment with massive, long-term multi-centre studies. Realistically, the incidence of most neonatal seizure etiologies is too low for running etiology-specific treatment studies in a single center within a reasonable time-frame. To be practical, trials may need to focus on multiple, related acute symptomatic etiologies (e.g. hypoxic–ischemic encephalopathy, arterial ischemic stroke, and intracranial hemorrhage), and assess antiseizure treatment separately for each etiology.

In a multi-center setting, it may be possible to recruit reasonable numbers in etiological subgroups that comprise the vast majority of all neonatal seizure cases (asphyxia, stroke and infection). Such a trial is challenged by the rapid and often erratic natural time-course of seizure occurrence. These seizures tend to disappear within tens of hours after onset, reducing rapidly the chances of capturing a treatment success [34]. The fluctuations in neonatal seizure occurrence drastically confound the assessment of short-term drug effects (within minutes or hours) as chance fluctuations may show apparent changes in seizure occurrence that are not a manifestation of the causal relationships with drug treatments. Careful inspection of seizure burden time-courses relative to drug dosing may inform a subjective judgement in individual cases (see Pressler et al. [11]); however, a therapeutic trial requires more objective comparisons with a control group of some kind. In hindsight, it is easy to speculate that many of the findings in past observational studies of neonatal seizure treatments may be erroneously reporting the spontaneous disappearance of seizures as treatment effects (see Stevenson et al. [34] for an example of this phenomenon in neonates and Goldenholtz et al. [35] for a similar result in adult epilepsy)

5. The critical tetrad: outcome measure, time delays, control group, and effect size

Once the cohort of interest and treatment protocol have been decided, investigators must consider four factors that will affect the sample size required for a successful trial: the outcome measure, the average time between drug administration and seizure onset, the type of control group, and the desired effect size (see Fig. 1). The effects of these factors on the sample size of the RCT have previously been evaluated using computer simulations; a technique which has become increasingly popular as an evidence-based tool for RCT design [34,36]. Simulation has shown that the required sample size increases rapidly when the trial uses positive control groups (i.e. an existing drug of some efficacy), targets a larger effect size, or if there is a longer delay from seizure onset to the drug administration. The choice of outcome measure, in conjunction with these other factors, may result in trial sample sizes ranging from tens to tens of thousands [34].

Moreover, the nonlinear effect of time delay on sample size (see Fig. 1) means that trials of a second-line drug require a large increase in sample size, particularly when testing

against an active treatment rather than placebo [34]. Increases in the required sample size are also apparent in cohorts treated with therapeutic hypothermia or other seizure-attenuating treatments, as the reduction in overall seizure burden reduces the potential treatment effect [37,38].

6. Logistic challenges call for alternative approaches

An evidence-based neonatal seizure trial design is theoretically possible by accounting for the implications of the critical tetrad described above. The practical constraints are, however, many: the numbers of infants available in one trial site are limited; there is a need for continuous prospective multi-channel EEG monitoring and its blinded visual analysis; the effect size may be small, making its reliable measurement difficult when EEG interpretation is subjective; it may be very challenging to run the trial protocol with sufficiently short time-delays in the midst of busy NICU routines. These constraints result in a rapidly escalating sample size to compensate for compromises in trial design. In this case, it becomes appealing to revisit alternative ways to perceive neonatal seizures.

Despite significant efforts in experimental and clinical studies, it has remained challenging to prove that neonatal seizures cause brain damage in the NICU setting, or to prove that effective neonatal seizure treatment improves neurocognitive outcomes [39,40]. In contrast, several clinical studies support the notion that seizures are associated with underlying brain damage and/or etiology, and the mere presence of seizures in the context of brain damage is predictive of neurocognitive outcome [41–43]. Therefore, neonatal seizures can be considered as a de-facto cot-side biomarker of newborn brain function.

Perceiving neonatal seizures as a biomarker rather than an object-to-treat would dramatically change views on seizure management. Such perception allows a more flexible, clinically adjusting, and context-aware (e.g. etiology specific) approach; the fundamental basis of modern personalized medicine. It would also lead to immediate opportunities for implementing automated seizure detection algorithms into clinical EEG monitors which is currently impeded by legal concerns relating to potential misdiagnosis, a worry caused by the implicit, yet unproven ethos among clinical community that neonatal seizures mandate treatment [5,27].

Modern day NICUs are already taking advantage of EEG monitoring of neonatal seizures for individualized neurological assessment (HIE scoring), therapeutic targeting, as well as early prognostication [44–47]. As a spin-off from this non-selective monitoring practice, it has recently become clear that non-pharmacological treatments, such as therapeutic hypothermia for HIE, may significantly reduce seizure burden, in addition to their known neuroprotective effects [37,38]. Such reductions in neonatal seizures increase the

difficulty of implementing neonatal seizure drug trials and reduce the clinical significance of any measured effects.

7. Conclusions

Assessing the efficacy of treatments for neonatal seizures is not a trivial task. Seizures are difficult to identify, highly variable (over time and over patients) and self-limiting. Furthermore, the very idea of trialing a treatment is overshadowed by a dearth of evidence on the causal relationship between seizures and neurodevelopmental outcome.

Analysis of previous RCTs combined with advances in our knowledge of the time-course of neonatal seizures provides insights that can aid future trial designs. We can now see that a control group is needed to measure the treatment effect, the choice of outcome measure is critical, and the outcome measure needs to be proximal enough to find any differences.

Although attempts to study individual drug effects on neonatal seizures may not translate ideally to clinical practice, future trials on infants with neonatal seizures will be challenged to define optimal holistic therapeutic conditions. In this case, seizures will be treated as a functional cot-side biomarker rather than as a disease per se, and the effect of therapy can be measured from the change in clinical outcomes rather than the occurrence of neonatal seizures.

Finally, the overall ideas in the present paper apply to any trial that aims to treat self-limiting symptoms, such as migraine, status epilepticus, lower back pain, or paediatric otitis [48–51].

Practice points

- Neonatal seizures present a challenging target for treatments due to their rapid natural time-course and high individual variability.
- Quantifying seizure burden from multi-channel EEG recordings is necessary to assess the efficacy of seizure treatment.
- The most important factors of choice in a neonatal seizure trial design include the outcome measure, the control group, and the delay from seizure onset to trial intervention.
- Trial design, notably the speed of trial protocol execution, will profoundly influence the required sample size.
- Trial simulations with etiology-specific seizure burden profiles are crucial for evidence-based trial design.

Research directions

- Characterization of the natural course of neonatal seizures in different etiologies.
- Building realistic simulations of neonatal seizures and trials.

- Prove the value of neonatal seizure treatment for neurodevelopment.
- Evaluate the use of neonatal seizures as a biomarker rather than as an object to treat.

Conflict of interest statement

None declared.

Funding sources

N.J.S. was supported by an EU Marie Skłodowska Action (H2020-MCSA-IF-656131). G.B.B. was supported by Science Foundation Ireland (12/RC/2272) and the European Union (FP7-HEALTH-2009-4.2-1, grant agreement 241479). S.V. was supported by Academy of Finland (#276523 and #288220), Sigrid Juselius Foundation, the European Union (FP7-HEALTH-2009-4.2-1, grant agreement 241479), as well as Lastentautien tutkimussäätiö.

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Fig. 1. Assessing neonatal seizure treatment drug efficacy and sample size in a randomized controlled trial. (A) Schematic examples of the temporal evolution of seizures for three potential treatments: a placebo control, positive control, and the trial drug. The time-periods used to calculate seizure burden are defined in the outcome measure. The outcome measure is compared between selected groups using a statistical test. (B) The effects of outcome measure (OM), control group, and time delays on the required sample size. OM1 is a trial that measures total recorded seizure burden in a neonate, OM2 is the seizure burden post treatment (assessed within a 12 h period), and OM3 is the relative reduction in seizure burden between a pre-treatment period (1 h) and post-treatment period (12 h). The upper bound is for a trial with positive controlled trial; the lower bound is for a placebo controlled trial. The simulated effect in this example is an 80% reduction in seizures for 72 h after treatment. Results are based on computer simulations of trials with seizure time-courses similar to that shown in Fig. 2. EEG, electroencephalography; SB, hourly seizure burden.

Fig. 2. The evolution of neonatal seizures from recorded seizure onset. (A) An example time-course of seizures in a neonate with hypoxic–ischemic encephalopathy (HIE); the hour-by-hour assessment of seizure burden (blue line) fluctuates unpredictably, but its general trend follows a lognormal curve with a rapid increase in seizure burden followed by a slow decay (black line). The hourly seizure burden has been calculated from the raw annotation of actual seizure occurrence (orange line). (B) Time-courses of neonatal seizures from a cohort of neonates with HIE (N = 41). Note the considerable variability in seizures over time and between neonates. (C) An alternative representation of the seizure time-courses in a subset of neonates with HIE (N = 21); each trace represents the seizure time-course from a single neonate where the width of the trace is proportional to the hourly seizure burden.